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GDTF: Generalized Detection Theoretic Framework for T-Wave Alternans Analysis

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ABSTRACT Detection and estimation of t-wave alternans (TWA) in presence of indispensable physiological artifacts is still a challenging task, as in most of the cases, the signal of interest resides well below the noise levels. In this paper, a generalized detection theoretic framework (GDFT) is proposed for the detection and estimation of TWA from the stress test ECG signal. The analytical foundations, TWA signal modeling, and finally simulations of nine TWA detectors and estimators belonging to median match filtering, empirical mode decomposition (EMD) based match filtering, and generalized likelihood ratio test (GLRT) for GDTF are presented. GLRT schemes require noise statistics for parameter estimation and are computationally efficient. GLRT detectors outperform all the detectors including the benchmark spectral method by $\geq$ 2 dB for a broad spectrum of SNR ranging from -15 dB to 30 dB under Gaussian noise. EMD based strategies also outperform spectral method under Gaussian and Laplacian noise by $\geq$ 1 dB.

INDEX TERMS T-wave alternans, sudden cardiac arrest, spectral methods, empirical mode decomposition, match filtering.

I. INTRODUCTION

Sudden cardiac death (SCD) is one of the leading causes of death in countries, even with the most advanced health care facilities. In the USA, for instance, approximately 50% of all deaths result from cardiovascular diseases. SCD is clinically defined as an unexpected death (within an hour of onset of symptoms) attributed to cardiac causes that may occur in a person with or without previous cardiac abnormalities. Micro-volt T-wave alternans (TWA) has been identified as a risk indicator for fatal cardiovascular arrhythmia including SCD [1]. TWA is a measure of variation in amplitude, shape, or phase of electrocardiogram (ECG) ST-T complex occurring in every alternative beat, also known as ventricular repolarization [2]. Macroscopic TWA phenomenon was discovered back in 1909 [3], however, due to very low incidence, macroscopic TWA only remained an ECG curiosity for some decades. Subsequently, the phenomenon was attributed to other clinical conditions as long QT syndrome, acute coronary ischemia, and electrolyte imbalance [4].

In the literature, TWA alternans refers to micro-volt TWA due to its linkages to ventricular arrhythmias leading to SCD.

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TWA linkage with the occurrence of ventricular tachycardia has been progressive and rapid due to advancements in signal processing techniques [5], [6]. TWA phenomenon can only be witnessed at an increased heart rate through an ECG stress test. Sensitive electrodes attached to the torso during the stress test pick various artifacts beside micro-volt TWA signals [7]. Due to these practical limitations, very low signal to noise ratio is achieved in cardiac signal acquisition as TWA is immersed in process noises [8]. Despite tremendous development in sensors technology, computational and signal processing techniques detection and estimation of TWA is still challenging.

TWA detection and estimation remained research focus and diverse methods have been proposed that can broadly be classified into two categories i.e., signal processing based methods and detection theoretic domains. Classical signal processing approaches involve pre-processing of ECG signal, subsequent transformation, detection of alternans, and finally reconstruction of varying ST-T segment and estimation of alternans voltage [9]. TWA are non-stationary because of the varying nature of statistical parameters over time [10]. However, optimum detection and estimation requires the signal to be stationary. Practically speaking, the signal is assumed to be stationary for a fixed number of beats of

ECG. Signal processing based techniques are further divided into time-domain, frequency-domain, and nonlinear filtering techniques. Prominent TWA detection schemes include spectral method (SM) [11] and modified moving average method (MMAM) [12]. The SM for quantitative analysis of TWA was incorporated in commercial equipment (CH2000, Bedford, MA, USA) for TWA clinical evaluation [4]. In [12], an alternative approach to the SM in time domain processing as MMAM is proposed that has been also incorporated in commercial testing equipment for TWA (CASE-8000, GE Medical Systems, Milwaukee, WI). SM and MMAM protocols have been approved by USA Food and Drug Administration (FDA) and are extensively used as benchmarks in clinical studies and research [13].

A diverse range of TWA analysis procedures based on advanced signal processing have also been reported. The prominent methodologies includes complex demodulation (CD) method [14], correlation method (CM) [15], Karhunen-Loève transform (KLT) [16], capon filtering (CF) method [17], Poincaré mapping (PM) method [18], and periodicity transform (PT) method [19]. In [9], the concise overview of these methods can be traced. In [20], PhysioNet in collaboration with Computers in Cardiology (CnC) presented annual challenge to measure TWA in a dataset of 100 electrocardiograms. The study presented an open source implementation of benchmark SM, analytical review of classical, and novel TWA analysis schemes, proposed improvement in existing methods and explored new methods. For the evaluation purpose, PhysioNet provided a dataset for experimentation including ECGs with reference rankings of TWA content. Critical analysis of top scoring algorithms suggested that a hybrid approach exploiting potentials of multiple approaches yields better sensitivity for detection and estimation of TWA. Recently, the detection theoretic domain has considerably evolved for TWA detection and estimation as a result of development in signal processing and computational sciences [21]. Research studies have shown that noise and signal probability density-based methods can improve TWA detection and estimation under varied noise scenarios [22]. TWA signal acquisition has a poor signal-to-noise ratio (SNR) due to various process noises, transient outliers, and physiological artifacts (e.g., electrode movement and muscular activity). Detection theoretic approaches are based on signal and noise assumptions viz-a-viz statistical parameter estimation. These methods primarily rely on noise modeling and signal probability density function (pdf) besides signal amplitude or energy. Detection theoretical approaches include maximum likelihood estimation (MLE), generalized likelihood ratio test (GLRT), and matched filtering.

In [22], the ECG noise statistics with a focus on the non-Gaussian nature of electrode movement and muscular activity noises are explored. Statistical analysis revealed that ECG noise and artifacts are heavily tailed and contain impulsive noise. Due to the leptokurtic distribution of electrode movement and muscular activity noises data, Laplacian distribution is assumed for noise realizations. Laplacian density function intrinsically presented robust statistics for electrode movement and muscular activity noises of ECG. Based on the Laplacian distribution assumption for process noises, a GLRT for TWA detection and estimation was derived. Simulation results showed that the GLRT detector based on Laplacian noise distribution outperformed SM. In [23], TWA detection under noise is further explored to account for non-stationary of electrode movement and muscular activity noises. During the course of experimentations, GLRT detector for TWA immersed in noise following Gaussian and Laplacian density functions have been tested for a broad spectrum of noise. Detection and estimation results of simulated TWA in real noise environments have proved the importance of prior knowledge of signal and noise probability densities for parameter settings of a good detector. Gaussian is a general assumption for any random process based on center limit theorem whereas the Laplacian model for noise is based on statistical analysis and experimental studies. Studies reveal that TWA detectors based on the Laplacian model caters for non-stationarity of noises and is more robust to outliers. In [24], the detection of signals with unknown parameters in the Gaussian noise of known covariance is analytically studied. The study revealed the asymptotic relation between GLRT test statistics and universally most powerful test (UMPT) for the Gaussian signal as the number of observations tends infinity or false alarm approaches zero. Studies in detection theoretic focused on matched filter based non-parametric bootstrap test, spatial filtering augmented Laplacian likelihood ratio method, and heart rate-adaptive filtering methods for TWA analysis [25]–[27].

In [28], the statistics and distributions of ECG noises of electrode movement and muscular activity are further explored. A statistical study of ECG noise recording from MIT BIH noise stress database revealed that the Laplacian model compromises the asymmetric nature of the probability distributions for electrode movement and muscular activity. Thorough statistical analysis presented bi-exponential distribution for modeling of electrode movement and muscular activity noises to cater for the leptokurtic as well as the asymmetric characteristics. Comparative analysis of the Laplacian model and bi-exponential model based on visual inspection, the goodness of fit, and Monte Carlo simulations prove the effectiveness of the model. The model achieves the best match of 99.14% and 98.13% for electrode movement and muscular activity as compared to a Laplacian fit of 95.20% and 93.84%, respectively. EMD based correlation methods, flutter detection in ECG, and template matched filter based on EMD methods have reported ECG and TWA analysis under a wide range of noise windows (-15 dB to 30 dB) [29], [30]. Hybrid techniques in detection theoretic employ EMD, correlation, and cross correlation-based signal processing algorithms for achieving the best of the two domains. Hybrid techniques in the detection theoretic also incorporate robust statistics for enhanced performance in the signal under noise. These schemes evolved considerably due to performance in a broad

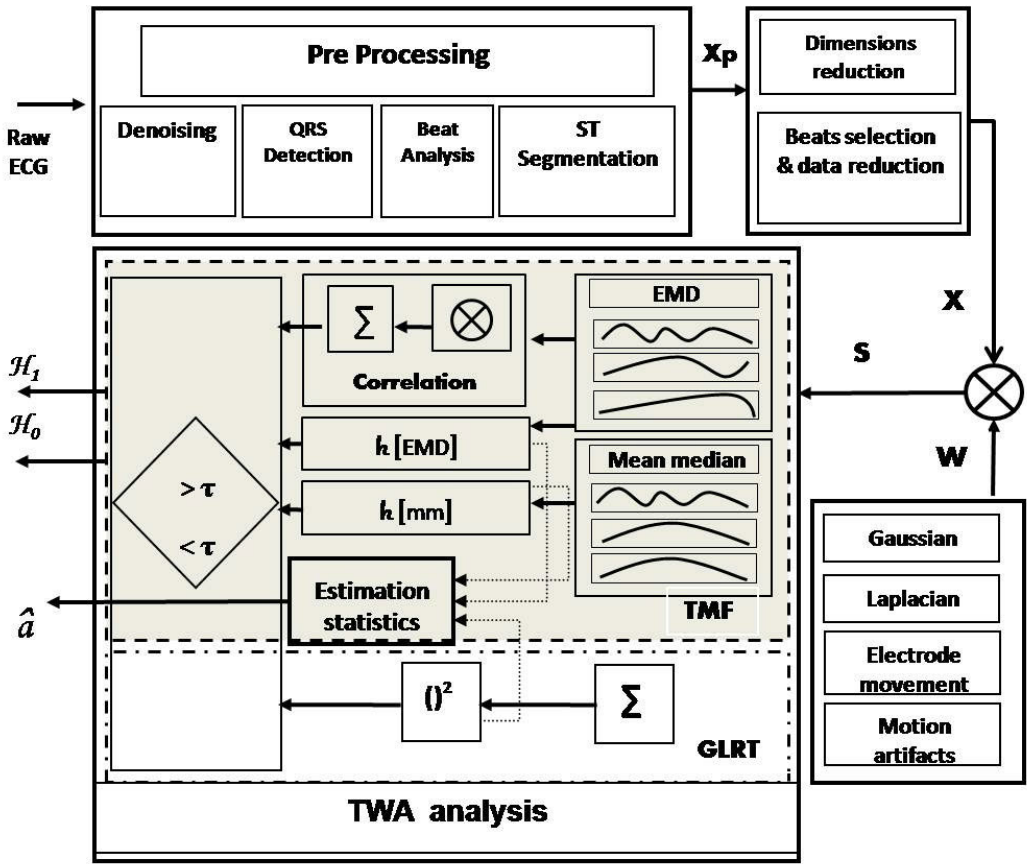

FIGURE 1. Schematic representation of various stages of the generalized detection theoretic framework.

spectrum of noise and consistency of performance under noise [31].

Analytical study in the detection theoretic domain for TWA analysis and related cardiac anomaly detection reveals that it caters for optimum detection under broader noise windows. To the best of our knowledge, there is a need to define a generalized detection theoretic framework for TWA analysis under noise, analytical foundations for signal and noise, parameter estimation for designing optimal detector, and finally performance evaluation strategy. In this paper, a generalized detection theoretic framework (GDTF) is presented based on signal under noise, statistical and probabilistic properties of signal to investigate realistic TWA acquisition under various physiological process noise artifacts. TWA of known amplitude is presented with a broad spectrum of realistic noise components to study the behavior of detection and estimation under different scenarios of process artifacts. Detection statistics and estimation have been worked out based on statistical signal theoretical foundations for a detector, estimator under various statistical parameters conditions. An analytical and holistic approach for the detection theoretic is presented with performance evaluation. SM and MMAM have been employed as benchmark for evaluation of TWA analysis. The major contribution of this study includes the proposal of a framework in detection theoretic context i.e., GDTF for TWA, reformulation of relevant existing techniques within the proposed framework, comprehensive analytical foundations for TWA detectors and estimator in GDTF, and performance evaluation of these detection theoretic approaches.

The rest of the paper is organized as follows. Section II presents the proposed GDTF, signal modeling for GDTF, theoretical foundation for generalized detector design followed by GLRT detector under various noise conditions, and match filtering with multiple templates. Section III deals with implementation strategy with mathematical foundations for optimal detection for GLRT detectors and templates based match filtering for signal under noise. Section IV is dedicated to results, performance comparison, and discussion. Section V concludes with elucidating future dimensions and potentials of GDTF.

II. GENERALIZED DETECTION THEORETIC FRAMEWORK

A. OVERVIEW

Statistical modeling of signal and noise is imperative for signal detection and estimation under noise. The GDTF for TWA analysis incorporates three stages i.e., pre-processing, data reduction, and TWA analysis as illustrated in Fig. 1. The input to GDTF is a raw ECG signal and output from the framework is detection information i.e., verdict about presence $\mathcal{H}_1$ or absence $\mathcal{H}_0$ of TWA, as well as amplitude of alternans. The details of each stage in GDTF are discussed in the following subsections.

1) PRE-PROCESSING

Pre-processing is standard practice for preparing the signal for posterior processing. Denoising is focused to minimize the process noises like baseline wander, electrode movement, and muscular activity. Baseline wander is a low-frequency artifact caused due to respiration, body movements, and electrode movement. Standard signal processing techniques like low-pass filtering and cubic spline interpolation are used to remove the baseline wander [32]. QRS detection is accomplished through a well establish Pan Hopkins algorithm [33], followed by ST onset and offset determination for the extraction of T-waves. Fiducial point determination is essential for using a reference for the measurement of T-wave alternans voltage. Ectopic beats are replaced with a null or moving average of neighboring beats. The outcome of the pre-processing stage is $\mathbf{X_p}$, which is a $N \times M$ matrix of ST-T segments.

2) BEAT SELECTION AND DATA REDUCTION

In the case of multi-lead TWA analysis, peak values of ST-T segments among multiple leads are calculated and subsequently sorted based on median and mean leads. Beat alignment is followed by leads selection. In the case of single lead analysis, if TWA amplitude is below a certain threshold value then the next set of beats is selected. Threshold is based on QRS complex detection and subsequent T-wave amplitude based on moving average. Beat alignment of valid beats and rejection of invalid beats is crucial for reducing the probability of false alarms. Beat alignment involves the selection of ECG lead for TWA, the establishment of fiducial point, and finally adjustment of fiducial point based on template beat selection. The template beat is usually the beat that is considered acceptable if the correlation on ST-T segment is higher than 0.8. In case of more than 10% of beats rejection, template beat is re-evaluated and the procedure is repeated for template beat selection.

For real-time ECG analysis using pattern recognition and machine learning, there is a need to pass only relevant features to the computational stage. In TWA detection and estimations schemes based on signal processing and detection theoretic domains, mostly data reduction is not employed as processing sample signal is maximum of 128 beats. However, in prognosis health management (PHM) systems based on real-time online data analysis require data reduction for efficient utilization of signal processing and storage resources of portable devices. Recent research on PHM involves high-dimensional datasets, multiple features set from multiple data sources, hence dimension reduction is a must step. Common data dimension reduction techniques use principal component analysis (PCA), linear discriminant analysis (LDA), canonical correlation analysis (CCA), and non-negative matrix factorization (NMF) [34]. Data reduction provides room for reducing the number of beat-to-beat series without loosing any information about TWA. It also reduces data redundancies in TWA as a signal is mostly concentrated between 0.3 Hz and 15 Hz. Data reduction transformations can be employed for the reduction of the coefficient vector. In some simple analytical schemes, no data reduction scheme is required [35], [36]. Data reduction can focus on the most relevant features by eliminating inefficient features. The output of this stage is a reduced data matrix i.e., $\mathbf{X}$.

3) TWA ANALYSIS

TWA analysis is a core and unique stage of GDTF where signal under noise is analyzed based on probabilistic and statistical signal models. The first null hypothesis is framed, where only the noise is assumed to be present. Subsequently, an alternative hypothesis is modeled, where both the signal and noise are taken into considerations. Statistical parameters of signal like mean, variance viz-a-viz noise probabilistic modeling help to predict the presence or absence of signal based on thresholding. Unknown signal parameters are substituted with maximum likelihood estimations for generalized statistics.

B. SIGNAL MODEL FOR TWA ANALYSIS

The signal of interest $\mathbf{X}$ is an $N \times M$ matrix of ST-T segments and is depicted as,

$$\mathbf{X} = [x_0, \cdots, x_{M-1}]^T, \tag{1}$$

where $\mathbf{x_m} = [x_m[0], \cdots, x_m[N-1]]$; $m = 0, \cdots, M-1$ is the m^{th} ST-T complex and N represents the number of data samples in each ST-T segment. For signal processing, an L beat analysis window of TWA extracted from M ST-T complexes, where $L \leq M$ can have following matrix notation,

$$\mathbf{S} = \mathbf{X} + \mathbf{W}, \tag{2}$$

where $\mathbf{W} \in \mathbb{R}^{\mathbb{N}\times\mathbb{L}}$ contains all types of process noises present in TWA.

The even and odd beats of ST-T segment are denoted as $\mathbf{E}, \mathbf{O} \in \mathbb{R}^{N\times L_2}$ respectively, and $\mathbf{x}_l, \mathbf{w}_l \in \mathbb{R}^{N\times 1}$ represents the l^{th} column of $\mathbf{X}$ and $\mathbf{W}$. We take the difference between $j = 0, 1, \cdots, L_2 - 1$ pairs of consecutive ST-T segments as $\mathbf{D} = [d_0, \cdots, d_{L_2-1}]$, where each column $\mathbf{d}_j$ is an N sample vector with n^{th} sample computed as a difference of j^{th} even and odd pair as,

$$d_j(n) = \left| o_j(n) - e_j(n) \right|. \tag{3}$$

Assuming $\mathbf{W}$ to be an uncorrelated additive white Gaussian process, we can write,

$$\mathbf{d}_j = \mathbf{u}_j + \mathbf{w}_j, \tag{4}$$

where $\mathbf{u}_j$ is the alternant waveform for j^{th} pair of ST-T segments and $\mathbf{w}_j$ is the vector of residue noise.

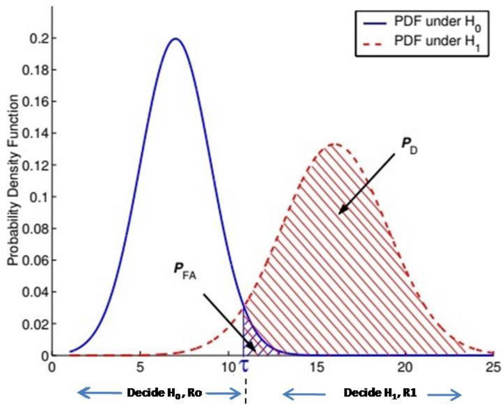

FIGURE 2. Detection theoretic based on probability densities of signal and noise viz-a-viz design parameters of detector.

C. DETECTOR DESIGN

1) THEORETICAL PRELIMINARIES

The standard hypothesis-testing problem for detecting j^{th} alternant signal is

$$\mathcal{H}_0 : \mathbf{d}_j = \mathbf{w}_j, \tag{5}$$
$$\mathcal{H}_1 : \mathbf{d}_j = \mathbf{u}_j + \mathbf{w}_j, \tag{6}$$

where $\mathcal{H}_0$ is the condition when detector only confronts noise, and $\mathcal{H}_1$ is the alternative scenario of alternans signal being embedded in the noise.

Based upon the probability of detection, the decision between $\mathcal{H}_0$ and $\mathcal{H}_1$ is taken by mapping the observed samples $[d_j[0], \cdots, d_j[N-1]]$ onto a decision regions R_0 and R_1 respectively as shown in Fig. 2. The probability of detection (P_D) of the j^{th} alternant waveform is computed as,

$$P_D = \int_{R_1} p(\mathbf{d}_j; \mathcal{H}_1)dx. \tag{7}$$

The detector compares the observed value with a threshold τ and maximizes the P_D, whereas minimizes the probability of false alarm (P_{FA}), which is calculated as,

$$P_{FA} = \int_{R_0} p(\mathbf{d}_j; \mathcal{H}_0)dx. \tag{8}$$

Neyman Pearson (NP) detector [37] maximizes the P_D by constraining P_{FA} to a fix value and decides $\mathcal{H}_1$ as,

$$Z_{LRT} = \frac{p(\mathbf{d}_j; \mathcal{H}_1)}{p(\mathbf{d}_j; \mathcal{H}_0)} > \tau \tag{9}$$

The NP detector also termed as likelihood ratio test (LRT) works as a trade-off between P_D and P_{FA}. In case the detection performance is poor, the threshold can be adjusted as $\acute{\tau}$ to further improve the detection. P_D and P_{FA} can then be calculated in terms of a monotonically decreasing function Q [38] as,

$$P_{FA} = Q\left(\frac{\acute{\tau}}{\sqrt{\frac{\sigma^2}{N}}}\right), \tag{10}$$

$$P_D = Q\left(\frac{\acute{\tau} - A}{\sqrt{\frac{\sigma^2}{N}}}\right), \tag{11}$$

where

$$\acute{\tau} = \sqrt{\frac{\sigma^2}{N}} Q^{-1}(P_{FA}). \tag{12}$$

Contrary to NP detection, the Bayesian detection approach [39] takes in to account the prior and conditional probability $P(\mathcal{H}_1|\mathcal{H}_0)$. $\mathcal{H}_1$is decided if,

$$Z_{\text{ML}} = \frac{p(\mathbf{d}_j|\mathcal{H}_1)}{p(\mathbf{d}_j|\mathcal{H}_0)} > \frac{P(\mathcal{H}_0)}{P(\mathcal{H}_1)} > \tau. \tag{13}$$

Like NP detector, test statistics is compared to a threshold, which is calculated from the prior probabilities. In case of TWA detection as a binary hypothesis testing, prior probabilities are equal or insignificant and detector decides $\mathcal{H}_1$ if,

$$p(\mathbf{d}_j|\mathcal{H}_1) > p(\mathbf{d}_j|\mathcal{H}_0). \tag{14}$$

This detector is termed as maximum likelihood (ML) detector as it chooses the condition with the larger conditional likelihood alternatively termed as maximum conditional likelihood detector (MCLD). NP detector compares the conditional probability to a threshold and decide $\mathcal{H}_1$. This also implies that

$$P(\mathcal{H}_1|\mathbf{d}_j > P(\mathcal{H}_0|\mathbf{d}_j). \tag{15}$$

The hypothesis is true for which the posterior probability is maximum and this type of detector is termed as maximum-a-posteriori (MAP). However, for equal prior probabilities MAP reduces to ML detector.

2) GENERALIZED LIKELIHOOD RATIO TEST (GLRT)

TWA signal is acquired in a stress test in which the patient is made to run on a treadmill or exercise on cycling while detectors pick the signal from the patient's body. During this test, the patient heart rate is increased from normal rate and various artifacts like muscular activity noise and electrode movement are also coupled with the acquired TWA signal. As the statistical properties of TWA and noise characteristics are unknown, therefore, Bayesian estimation is not feasible. The scenario is known as composite hypothesis testing, where parameter values are unknown. In this case, GLRT can be used as a locally most powerful (LMP) detector. The detector design with signal and its parameters constraints under binary and composite hypothesis testing is shown in Fig. 3.

Statistical parameters of TWA are usually unknown and need to be assessed for GLRT processing using the MLE procedure. The method selects the set of values of the model parameters that maximize the likelihood function. The estimation is dependent on assumptions about signal pdf and noise characteristics. The estimated parameter values improve as the number of observations increases. The mean and variance of TWA can be estimated by taking mean and variance as parameters and finding particular parameter values that make the observed result most likely for a given

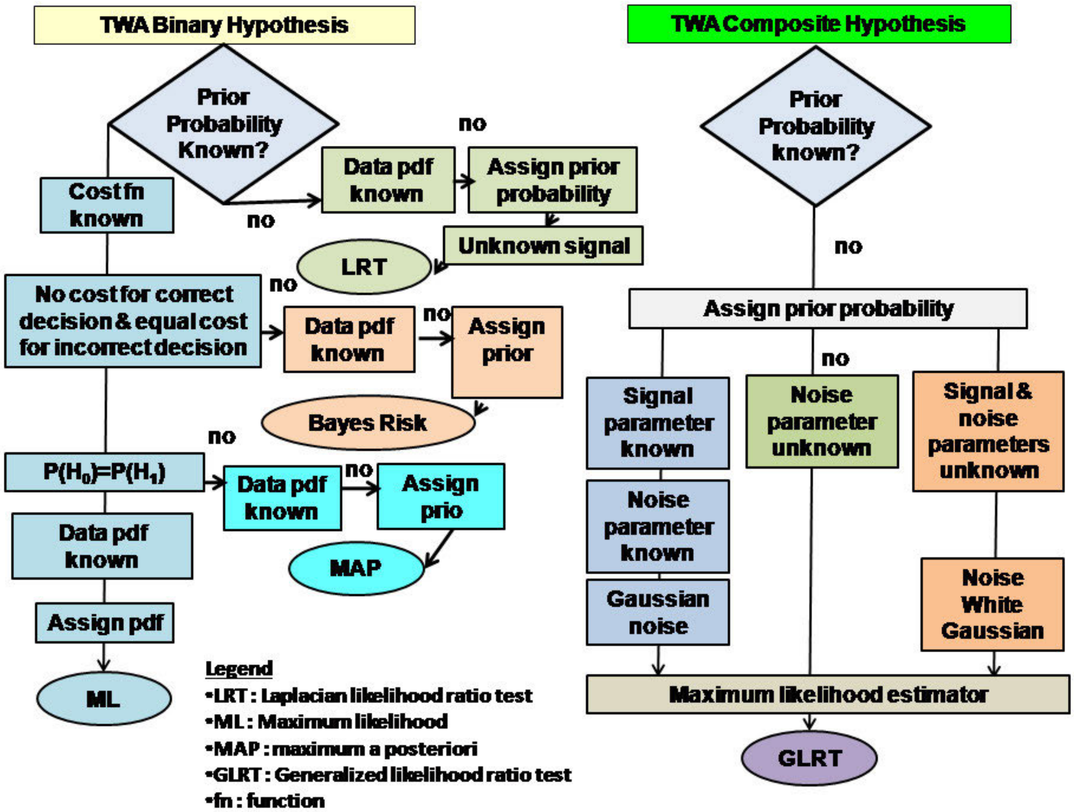

FIGURE 3. TWA detector design with signal parameter constraints in binary and composite hypothesis testing.

model. Let Z_{GLRT} is the likelihood ratio of the two probability distributions and is written as,

$$Z_{GLRT} = \frac{p(\mathbf{d}_j; \hat{\theta}_1 \mathcal{H}_1)}{p(\mathbf{d}_j; \hat{\theta}_0 \mathcal{H}_0)} > \tau \tag{16}$$

where $\hat{\theta}_1$ and $\hat{\theta}_0$ are maximum likelihood estimates of unknown parameters of TWA.

MLE is used to estimate the amplitude of the detected TWA based on the assumption that noise is embedded in the signal. Let n be the independent and identically distributed observations of TWA samples $\mathbf{d}_j[0], \cdots, \mathbf{d}_j[N-1]$ following probability distribution function p, where θ is a vector of unknown parameters and referred as the true value of the parameter vector. The joint distribution $p(\mathbf{d}_j : \theta)$ for all observations is calculated as,

$$p(\mathbf{d}_j : \hat{\theta}) = p((\mathbf{d}_j[0], \cdots, \mathbf{d}_j[N-1]) = \prod_{i=1}^{N} p(\mathbf{d}_j; \hat{\theta}_0). \tag{17}$$

This function $p(\mathbf{d}_j : \hat{\theta}_0)$ is likelihood function of X. The maximum likelihood estimate is the value that maximizes $p(\mathbf{d}_j : \theta)$. θ is a vector of p components $\theta = (\theta_1, \theta_2, \ldots \theta_p)$ and grad operator is defined as,

$$\nabla_\theta = \begin{bmatrix} \frac{\partial}{\partial \theta_1} \\ \frac{\partial}{\partial \theta_2} \\ \vdots \\ \frac{\partial}{\partial \theta_p} \end{bmatrix} \tag{18}$$

For ease of analytical evaluation and calculation, log likelihood function is defined as,

$$l(\theta) = \ln p(\mathbf{d}_j; \theta). \tag{19}$$

As logarithm is a monotonically increasing function, therefore, maximizing log likelihood function also maximizes θ as,

$$\hat{\theta} = arg\ max_\theta\ l(\theta). \tag{20}$$

The multiplication of n joint probabilities is simplified due to logarithmic property as,

$$l(\hat{\theta}) = \sum_{k=1}^{k=n} \ln p(\mathbf{d}_j;\ \theta), \tag{21}$$

where parameters set $\hat{\theta}$ is referred unbiased once its mean value is true value of unknown parameter. As MLE for every

TABLE 1. TWA detection statistics and estimation for various schemes in GDTF.

Methods	Assumptions	Detection	Estimation
Neyman Pearson [39]	Pdfs of under both hypothesis known	$Z_{LRT} = \frac{p(\mathbf{d}_j;\mathcal{H}_1)}{p(\mathbf{d}_j;\mathcal{H}_0)} > \tau$	$\hat{a} = N\sum_{n=0}^{N-1}(\mathbf{d}_j[n]\mathbf{u}_j[n])$
Maximum likelihood [37]	Prior probabilities known or equal priors	$Z_{\mathrm{ML}} = \frac{p(\mathbf{d}_j\|\mathcal{H}_1)}{p(\mathbf{d}_j\|\mathcal{H}_0)} > \frac{P(\mathcal{H}_0)}{P(\mathcal{H}_1)} > \tau$	$\hat{a} = N\sum_{n=0}^{N-1}(\mathbf{d}_j[n]\mathbf{u}_j[n])$
Generalized likelihood [24]	Maximum likelihood estimates can be evaluated	$Z_{GLR} = \frac{p(\mathbf{d}_j;\hat{\theta_1}\mathcal{H}_1)}{p(\mathbf{d}_j;\hat{\theta_0}\mathcal{H}_0)} > \tau$	$\hat{a} = N\sum_{n=0}^{N-1}\mathbf{d}_j[n]\mathbf{u}_j[n])$
GLRT-Gaussian [17]	Noise is Gaussian with mean μ and variance σ known	$Z_{\mathrm{GLRg}} = \sum_{n=0}^{N-1}(\mathbf{d}_j[n]\mathbf{u}_j[n])^2 > \tau$	$\hat{a} = \frac{1}{N}\sum_{n=0}^{N-1}\frac{(\mathbf{d}_j[n]\mathbf{u}_j[n])}{(\mathbf{u}_j[n])^2}$
GLRT-Laplacian [22]	Noise is Gaussian with mean μ and variance σ known	$Z_{\mathrm{GLRl}} = \sqrt{\frac{32}{\sigma^2}}\sum_{n:0<\mathbf{d}_j<\mathbf{d}_{med}}\mathbf{d}_j[n] > 0$	$\hat{a} = Median(\mathbf{d}_j[n]\mathbf{u}_j[n])$
Matched filter [40]	Template of signal available or can be estimated	$Z_{TMF} = \boldsymbol{u}_j^T\boldsymbol{g}_i$	$\hat{a} = N\sum_{n=0}^{N-1}\mathbf{d}_j[n]\mathbf{u}_j[n])$
SM [41]	Noise estimation as per SM noise window	$Z_{\mathrm{SM}} = \sum_{n=0}^{N-1}(\mathbf{d}_j[n]\mathbf{u}_j[n])$	$\hat{a} = \frac{1}{N}\sum_{n=0}^{N-1}(\mathbf{d}_j[n]\mathbf{u}_j[n])$

data set N converges mean values to true value of unknown parameters, therefore, MLE is asymptotically unbiased. MLE also holds the property of asymptotically consistent as it is probable that the estimate is close to true value for large N.

D. TWA ESTIMATION

TWA estimation in the presence of process noises is a more tedious task as compared to its detection because of numerous challenges. Some of these challenges faced during TWA analysis include, very small alternans magnitude ($1.9\mu V$ is clinically significant) to be detected and estimated, physiological artifacts including electrode movement and muscular activity distort the ECG signals, baseline wander causes the entire ECG signal to shift from its normal base, and artifact data (respiration and electrode movement) introduced into actual cardiac activity. As signals are recorded during exercise and if ST-T segmentation based on QRS detection have errors then it results in wrong detection or prior estimation results. Moreover, no gold standard exists for evaluation of TWA detection and estimation. As estimator is a function of probability distribution of observations set, therefore, estimation accuracy improves as the number of realization are increased. For GDTF, a generalized TWA estimator is a function of pdf of data observations immersed in noise as,

$$\hat{a} = \nabla(\mathbf{u}_j, \mathbf{w}_j) \tag{22}$$

where $\nabla(\cdot)$ is the maximum likelihood estimate of alternant waveform $\mathbf{d}_j$. In GDTF scenario, parameters worked out for evaluation of estimation accuracy include standard deviation σ, estimation bias β, and mean square error ξ, which are calculated as,

$$\sigma = \sqrt{\frac{\sum_{i=0}^{n}(a_i - \bar{a})}{n}}, \tag{23}$$

$$\beta = \frac{\sum_{i=0}^{n}(a_i - a)}{n}, \tag{24}$$

$$\xi = \frac{\sum_{i=0}^{n}(a_i - a)^2}{n}, \tag{25}$$

where n is the total umber of trails, a actual alternans magnitude, $\bar{a}$ is mean of estimated mean, and a_i is the estimated value in i^{th} trial.

III. GDTF IMPLEMENTATION

The methods, assumptions, detection theoretic, and estimation statistics for implementation within GDTF are presented in TABLE 1. The steps followed to implement GDTF is presented as Algorithm 1.

Algorithm 1 Algorithm for TWA Analysis in GDTF

Input : Raw ECG $x[n]$

Output: Detection statistics $\mathcal{H}_0$ or $\mathcal{H}_1$and Estimation statistics: $\hat{a}$

1) Extract raw ECG vector $x[n]$
2) Denoise ECG: Bandpass filtering, 50 Hz notch filter, cubic spline interpolation for baseline correction
3) Check for missing beat and replace with mean value of previous n beats
4) Delineate ECG, detect R peaks, onset of S, peak of T, offset of T
5) Process dimension reduction and ECG lead selection for multiple leads ECG input
6) Extract L beats of ST-T segments as matrix $\mathbf{X}$
7) Add noise from MIT-BIH Arrhythmia database
8) Apply detection and estimation statistics (H_0 or $\mathcal{H}_1$ and $\hat{a}$) G
9) Estimate error and evaluation of results

A. OPTIMAL DETECTION - GLRT UNDER VARIOUS NOISE ASSUMPTIONS

In statistical modelling of TWA immersed in noise, the most generic assumption as per statistical signal processing is Gaussian and Laplacian, which are discussed in following subsections.

1) GLRT-GAUSSIAN

Let TWA of unknown amplitude is immersed in process noises and further assume noise as white Gaussian i.e., $\mathbf{d}_j \sim N(\mu, \sigma)$. MLE technique can be used to estimate amplitude $\hat{a}$ of TWA using Eq. (20) as,

$$\hat{\theta} = arg\ max_\theta \left\{p(\mathbf{d}_j; \hat{a})\right\} \tag{26}$$

The Gaussian function can be expended as,

$$\hat{\theta} = arg\ max_\theta \times \left\{\frac{1}{(2\pi)^{N/2}(\sigma)^{N/2}} \exp\left\{-\frac{1}{2(\sigma)^2}\sum_{n=0}^{N-1}(\mathbf{d}_j[n] - \hat{a}\mathbf{u}_j[n])^2\right\}\right\} \tag{27}$$

For simplification of analytical function, logarithmic function can be used as,

$$ln(\hat{\theta}) = arg\ max_\theta ln\left[\left\{\frac{1}{(2\pi)^{N/2}(\sigma)^{N/2}} \times \exp\left\{-\frac{1}{2(\sigma)^2}\sum_{n=0}^{N-1}(\mathbf{d}_j[n] - \hat{a}\mathbf{u}_j[n])^2\right\}\right\}\right] \tag{28}$$

Maximizing the above function can maximize $ln(\hat{\theta})$ over $\hat{a}$ or alternatively minimize exponent function as,

$$\kappa(\hat{a}) = \frac{1}{2(\sigma)^2}\sum_{n=0}^{N-1}(\mathbf{d}_j[n] - \hat{a}\mathbf{u}_j[n])^2. \tag{29}$$

For minimum value of $\kappa(\hat{a})$ setting $\frac{\partial\kappa(a)}{\partial\hat{a}} = 0$ results in

$$\hat{a} = \frac{1}{N}\sum_{n=0}^{N-1}\frac{(\mathbf{d}_j[n]\mathbf{u}_j[n])}{(\mathbf{u}_j[n])^2}. \tag{30}$$

By using Eq. (16) to find test statistics Z_{GLRG} to decide $\mathcal{H}_1$ as,

$$Z_{\mathrm{GLRG}} = \frac{\frac{1}{(2\pi)^{N/2}(\sigma)^{N/2}}\exp\left\{-\frac{1}{2(\sigma)^2}\sum_{n=0}^{N-1}(\mathbf{d}_j[n]-\hat{a}\mathbf{u}_j[n])^2\right\}}{\frac{1}{(2\pi)^{N/2}(\sigma)^{N/2}}\exp\left\{-\frac{1}{2(\sigma)^2}\sum_{n=0}^{N-1}(\mathbf{d}_j[n]\right\}} > \tau \tag{31}$$

By taking logarithm and simplifying Z_{GLRG} can be written as,

$$Z_{\mathrm{GLRG}} = -\frac{1}{2(\sigma)^2}\sum_{n=0}^{N-1}(-2\hat{a}\mathbf{u}_j[n]\mathbf{d}_j[n] + 2a^2\mathbf{u^2}_j[n]) > \tau \tag{32}$$

By using value of $\hat{a}$ from (Eq. (30)), test statistics to decide can be written as,

$$Z_{\mathrm{GLRG}} = \sum_{n=0}^{N-1}(\mathbf{d}_j[n]\mathbf{u}_j[n])^2 > \tau. \tag{33}$$

2) GLRT-LAPLACIAN

The Gaussian model based on center limit theorem simplifies the analytical detection. However, it does not represent the realistic assumptions due to outliers in real ECG noises. The presence of outlier and the statistical investigation reveals that the Laplacian distribution is more viable for noise assumptions [22]. If we compare Gaussian and Laplacian models, the first two moments have similarities as both have zero mean. The Laplacian noise produces spikes of very high amplitudes and outliers that need to be catered for a good TWA detector. The comparison reveals that the Laplacian detectors have very high amplitude around mean values also referred as spikes. The detection of TWA is very critical and if the detector fails to tackle these non-linearities, it may mislead the physicians. The degree of non-Gaussian of a zero-mean pdf is characterized in terms of its kurtosis relative to Gaussian pdf as,

$$\psi_2 = \frac{E(w^4[n])}{E(w^2[n])}. \tag{34}$$

For Gaussian pdf kurtosis ψ_2 values lies around zero and for Laplacian it is greater than zero. Let TWA is to be detected in white noise following Laplacian distribution, for the same model Eq. (4)) can be represented as,

$$p(\mathbf{d}_j; a, \mathcal{H}_1) = (\frac{1}{2\sigma^2})^{\frac{N}{2}} \exp\left(\sqrt{-\frac{2}{\sigma^2}}\sum_{n=0}^{N-1}\left|\mathbf{d}_j[n]-\hat{a}\mathbf{u}_j[n]\right|\right) \tag{35}$$

For MLE of unknown amplitude $\hat{a}$, minimum value of,

$$\theta = \left|\mathbf{d}_j[n] - \hat{a}\mathbf{u}_j[n]\right| \tag{36}$$

N is assumed to be even for simplicity of derivation and also note that $\theta(\hat{a})$ is differentiable except at points $[\mathbf{d}_0, \mathbf{d}_1 \ldots, \mathbf{d}_{N-1}]$. Excluding these points we have,

$$\frac{\partial\theta(\hat{a})}{\partial\hat{a}} = -\sum_{n=0}^{N-1} sgn(\mathbf{d}_j[n] - \hat{a}\mathbf{u}_j[n]) \tag{37}$$

As $sgn(\mathbf{d}_j[n] - \hat{a}\mathbf{u}_j[n]) = 1$, if $\hat{a} < \mathbf{d}_j[n]$ and $sgn(\mathbf{d}_j[n] - \hat{a}\mathbf{u}_j[n]) = -1$, if $\hat{a} > \mathbf{d}_j[n]$. Therefore, it can be shown that $\frac{\partial\theta(\hat{a})}{\partial\hat{a}} = 0$, if it is chosen as median of the data samples. Exclusion of the data points from minimization can be justified due to convexity of the system. MLE of a, $\hat{a} = \mathbf{d}_j[n]_{med}$ and GLRT decides $\mathcal{H}_1$ as,

$$2ln(\theta) = ln\frac{p(\mathbf{d}_j[n]; \mathbf{d}[n]_{med}, \mathcal{H}_1)}{p(\mathbf{d}_j[n]; \mathcal{H}_1)}, \tag{38}$$

$$2ln(\theta) = -2\sqrt{\frac{2}{\sigma^2}}\sum_{n=0}^{N-1}\left|\mathbf{d}_j[n] - \mathbf{d}[n]_{med} - \mathbf{d}_j[n]\right| > ln\gamma \tag{39}$$

To simplify the test statistics, the data samples can be arranged in ascending order than median between $\mathbf{d}_j[\frac{N}{2}-1]$ and $\mathbf{d}[\frac{N}{2}]$, which can be represented as,

$$\mathbf{d}_{med} = \frac{\mathbf{d}[\frac{N}{2}-1]+\mathbf{d}[\frac{N}{2}]}{2} \tag{40}$$

As the sum of numbers is independent of ordering so GLRT test statistics can be written as,

$$2ln(\theta) = \sqrt{\frac{8}{\sigma^2}}\sum_{n=0}^{\frac{N}{2}-1}(\left|\mathbf{d}_j[n]\right| + (\mathbf{d}_j[n]) + \sqrt{\frac{8}{\sigma^2}}\sum_{n=\frac{N}{2}}^{N-1}(\left|\mathbf{d}_j[n]\right| - (\mathbf{d}_j[n]) \tag{41}$$

In the above equation, if $\mathbf{d}[n]_{med} > 0$ than all the data samples have positive values and sum of second portion is zero. Similarly, in the case of negative values the first potion of above equation is zero. Based on this observation, test statistics Z_{GLRL} can be further simplified as,

$$Z_{\text{GLRL}} = \begin{cases} \sqrt{\frac{32}{\sigma^2}}\sum_{n:0<\mathbf{d}_j<\mathbf{d}_{med}}\mathbf{d}_j[n] & if\ \mathbf{d}_{med} > 0 \\ -\sqrt{\frac{32}{\sigma^2}}\sum_{n:0<\mathbf{d}_j<\mathbf{d}_{med}}\mathbf{d}_j[n] & if\ \mathbf{d}_{med} < 0. \end{cases} \tag{42}$$

B. TEMPLATE BASED MATCHED FILTERING (TMF)

The match filtering technique is an optimal linear filter that maximizes the SNR in the presence of known stochastic noise. We employ this method to detect the presence of TWA in known noise statistics. The template of the signal is very critical for maximizing SNR at the output for optimal detection. The test statistics Z_{TMF} can be represented as,

$$Z_{TMF} = \boldsymbol{u}_j^T\boldsymbol{g}_i, \tag{43}$$

where $\boldsymbol{u}_j^T$ represents the transpose operation of given vector and finite impulse response of the equation gives maximum SNR at the output to ensure the optimal detection of TWA. The match filter test statistics directly depends on the product of difference of even and odd beats $\mathbf{u}_j$ and residual noise $\mathbf{w}_j$. The residual noise is in a way directly related as minimizing its effect shall increase the detection. The TWA waveform is although deterministic, however generally unknown, therefore the proposed detector (Eq. (43)) is classically not optimal. In GDTF, $\boldsymbol{g}_i$ has a direct bearing on the detection statistics of the matched filter. Template based match filtering utilizing mean and median of TWA as suggested in [40] has also been included in performance evaluation.

C. EMD BASED MATCHED FILTERING (TMF_{EMD})

EMD is a recently developed technique for decomposing a signal into its basic constituents. It works in the time domain and is a purely data-driven empirical method. EMD has been explored to reveal the physics behind the non-linear and non-stationary natural signals like ECG. The technique is at par with analytical techniques like Fourier transform and wavelet decomposition. Moreover, it does not require any prior information or non-stationary assumptions as required in Fourier transform and wavelet-based methods. It works on the fact that any complicated dataset can be transformed into small and simple data subsets known as intrinsic mode functions (IMFs). The IMFs are extracted based on a process known as sifting process, which first identifies local maxima, connects through a cubic spline to trace the upper envelope. The process is repeated with minima points in test data to trace minima points of the lower envelope. [42].

In our problem of TWA signal $\mathbf{X}$, EMD decomposition involves the identification of all local maxima and minima points of a test signal. To trace the data, need to join the maxima and minima points through a cubic spline. Let the locus of the upper envelope traced by maxima points be represented as $\mu[n]$ and minima points function as $\eta[n]$. The mean of the two functions is represented as,

$$\phi[n]_1 = \frac{\mu[n]+\eta[n]}{2}. \tag{44}$$

TWA signal's first proto-IMF $\xi_1(n)$ is obtained by subtracting mean value from as,

$$\xi(n) = (\mathbf{u}_j[n]+\mathbf{w}_j[n]) - \phi[n]_1 \tag{45}$$

The process iteration yields n number of IMFs i.e., $\xi_1(n)$ to $\xi_n(n)$, and a residue function $\gamma[n]$. Finally, TWA signal is represented as,

$$y[n] = \sum_{j=1}^{n}\xi_j(n) + \gamma[n]. \tag{46}$$

EMD is an iterative process, stoppage criteria set the threshold between alternative iterations for determination of IMF. The normalized squared difference after each iteration is compared to a pre-set threshold for evaluation of IMFs. Each IMF represents the oscillatory component of TWA and Hjorth descriptors, which are used as a measure of spectral purity index (SPI) of IMF. The pure sine function is assigned the maximum value of SPI i.e., 1. Based on individual SPI indices of each IMF, the TWA signal is reconstructed by discarding the noise components. The Hjorth descriptors represent the power spectral moments of the signal under noise i.e., TWA. SPI indices are evaluated as,

$$SPI = \frac{1}{1+(\lambda_2/\lambda_1)^2}, \tag{47}$$

where λ_1, λ_2 represents mobility and complexity parameters of Hjorth descriptors.

IV. EXPERIMENTAL RESULTS

In this work, we have implemented three approaches, which are as follows.

- In EMD signal reconstruction using SPI, parameters set including activity, mobility, and complexity used as a criterion for distinguishing signal from noise [43]. SPI indices are evaluated from Hjorth descriptors and gives an insight into the spectral moments of the power spectrum in the time domain. A pure sine wave is a spectral benchmark for SPI indices as it holds maximum value. SPI of all decomposed signals with EMD and residue of the signal are evaluated based on the SPI index and signal is reconstructed and noise IMFs are discarded.

- In a cross-correlation approach for the TWA signal with decomposed components of EMD for the identification of signal and noise components, the signal is more correlated with individual IMFs. Whereas noise does not correlate as it has a different origin. In the case of TWA, the main sources of noise are a relative movement of electrodes attached with the body, variation in sensor conductivity due to preparation, and EMG noise due to muscular activity. The cardiac signal originates from pacemaker cells in the sino-atrial node has a different origin than noise.
- In other variants of EMD decomposition and reconstruction of TWA signal component and rejection of noise is achieved with the help of Hurst exponents. This parameter is known as an index of dependence as it quantifies the relative tendency of a time series to the mean value. It is designated by H and value in range 0.5-1 indicates a positive correlation. TWA signal and noise components are segregated based on H index [31].

A. SETUP FOR EXPERIMENT AND SIMULATION

Background ECG signal is generated from heartbeat streams arbitrarily obtained from ECG signals of MIT-BIH arrhythmia database publicly accessible from MIT Physionet [44]. To validate the performance of TWA detection and estimation under generalized and realistic scenarios, real ECG signals with Gaussian and Laplacian noise are also synthesized. Fig. 4 illustrates the simulated TWA signal detection and estimation for the SNR range of -15 dB to 30 dB under GDTF.

A simplified simulated problems of TWA detection under noisy environment is also considered. For this purpose, TWA is simulated as a Hamming window of unit amplitude immersed in WGN. As for null hypothesis Eq. (5) and alternative hypothesis Eq. (6) in a scenario of binary detection problem. Contrary to classical signal processing framework like SM [41], MMAM [12], and CM [15] where decision is based on complet set of beats of TWA, in the proposed GDTF, each beat is mapped onto a decision regions R_0 or R_1 based on a threshold that maximizes Eq. (8). Conversely, Eq. (8) constrains defines a boundary for partition of data space Eq. (1) into $R_0 = \{\mathbf{X} : \textit{decide } \mathcal{H}_0 \textit{ or reject } \mathcal{H}_1\}$ or $R_1 = \{\mathbf{X} : \textit{decide } \mathcal{H}_1 \textit{ or reject } \mathcal{H}_0\}$. In such statistical problems, various probabilistic solutions exits that satisfies R_0 or R_1, however the optimum is the one that maximizes Eq. (7). The detection problem transforms into a mapping criterion based on signal and noise parametric assumptions viz-a-viz detection strategy. GDTF design cycle begins by setting a P_{FA} as per Eq. (8) and increasing threshold reduces P_{FA}. The second critical parameter P_D can be related to P_{FA} as Q function is monotonically decreasing function since $1-Q$ is

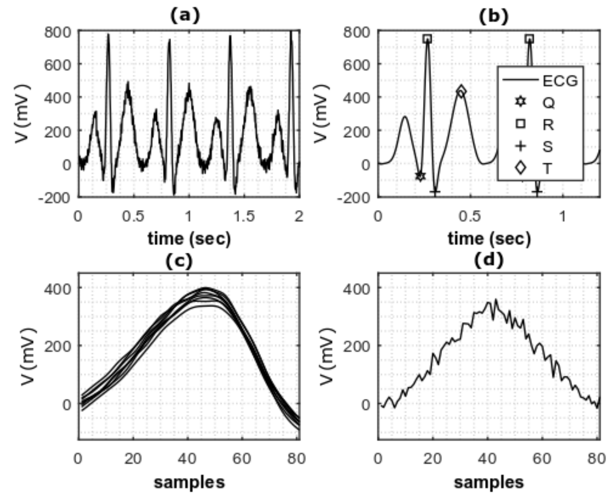

FIGURE 4. ECG signal synthesis for TWA analysis (a). Raw ECG signal with process noises (b) ECG PQRTS wave delineation after denoising (c) Extraction of T-wave and alignment of waves(d) Signal with TWA alternans as test signal for experimentations.

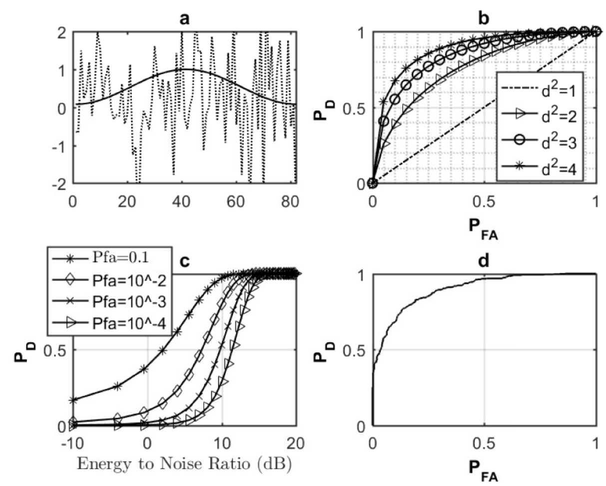

FIGURE 5. (a) Simulated TWA in Gaussian noise (b) Probability of detection and false with deflection coefficient (c) Probability of detection and false alarm tuning (d) Receiver operating curve.

a cumulative distribution function (CDF) and monotonically increasing function. Detection performance is also characterized by deflection coefficient d^2, which is dependent on signal mean value and inversely related to the variance of noise as depicted in Fig. 5 (b). Finally, Fig. 5 (d) explains the DTF strategy for optimum parameters, which returns the receiver operating characteristics curve (ROC).

B. PERFORMANCE ANALYSIS UNDER GAUSSIAN NOISE

Detection and estimation of TWA in white Gaussian i.e., $\mathbf{d}_j \sim N(\mu, \sigma)$ has been evaluated for a set of template-based matched filters, match filtering using EMD using SPI and correlations [31]. Monte Carlo simulation results for the entire noise band from -15 dB to 30 dB for detection under Gaussian noise are presented in Fig. 6. Estimation bias, mean square error, and relative estimation bias results are depicted in Fig. 6(b), Fig. 6 (c), and Fig. 6 (d) respectively. TMF

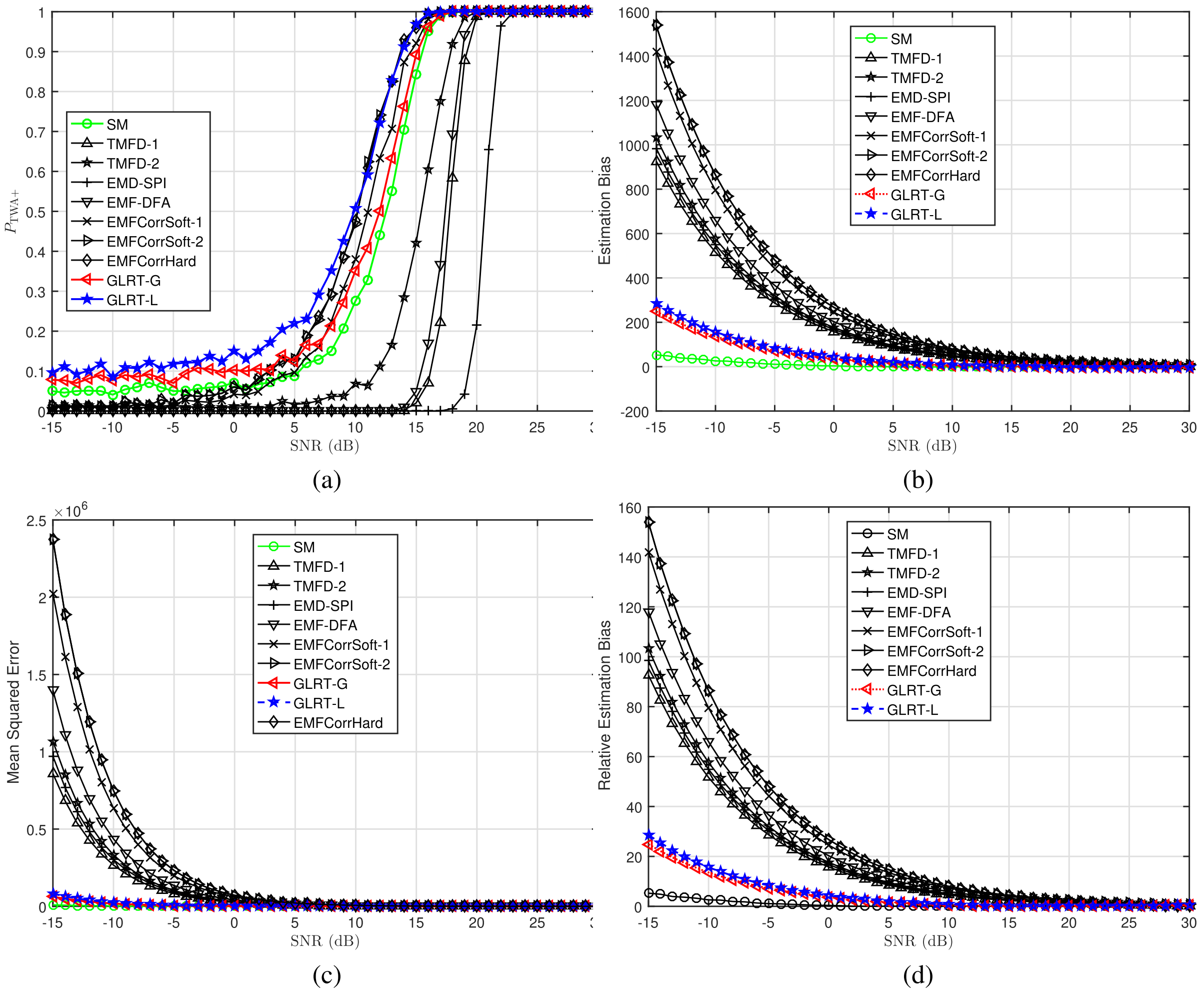

FIGURE 6. **GLRT detectors performance for 10 μV TWA under Gaussian noise, (a) Detection (b) Estimation (c) Mean square error (d) Relative estimation bias.**

based on mean and median works for SNR $\geq$ 15 dB as detection is based on template formed from signal under noise. EMD decomposition and correlation-based strategies provide better TWA signal detection than TMF based on mean and median. These variants also outperform detection by SM. The GLRT estimators outperform all estimators in GDTF and follow the trend of benchmark SM estimator in performance.

C. PERFORMANCE ANALYSIS UNDER LAPLACIAN NOISE

The statistical study of TWA acquisition process noises due to muscular activity and electrode movement reveals that the Laplacian model is more realistic than Gaussian approximation [22]. Monte Carlo simulation for TWA detection and estimation under Laplacian noise is also conducted, which is shown in Fig. 7. EMD strategies based on correlation outperform all other approaches including GLRT based approaches. EMD based techniques also outperform SM, a traditional benchmark for TWA analysis. TWA real noises muscular activity and electrode movement follow a Laplacian probability distribution. GLRT estimators outperform and estimation results are comparable to benchmarked SM estimator. It is also noted that estimation is significantly lower under adverse signal conditions (SNR $<$ 0 dB), comparative estimation bias is rendered irrelevant. Therefore, under GDTF, a more meaningful estimator comparison warrants observation of bias under better signal quality with the probability of true positive $\geq$ 0.99. GLRT approaches present comparatively better estimation than TMF based on correlation-based schemes.

D. COMPUTATIONAL ANALYSIS

Being a data-driven method, decomposition of the signal into a finite number of IMFs, establishing correlation indices, and finally, reconstruction of the signal from selected IMFs involve computational complexity. The detection performance of these schemes is directly related to the computational complexity and run time. GLRT methodologies based on Gaussian noise statistics outperforms SM by $\geq$ 2 dB, as well as, all TMF based strategies. These strategies are

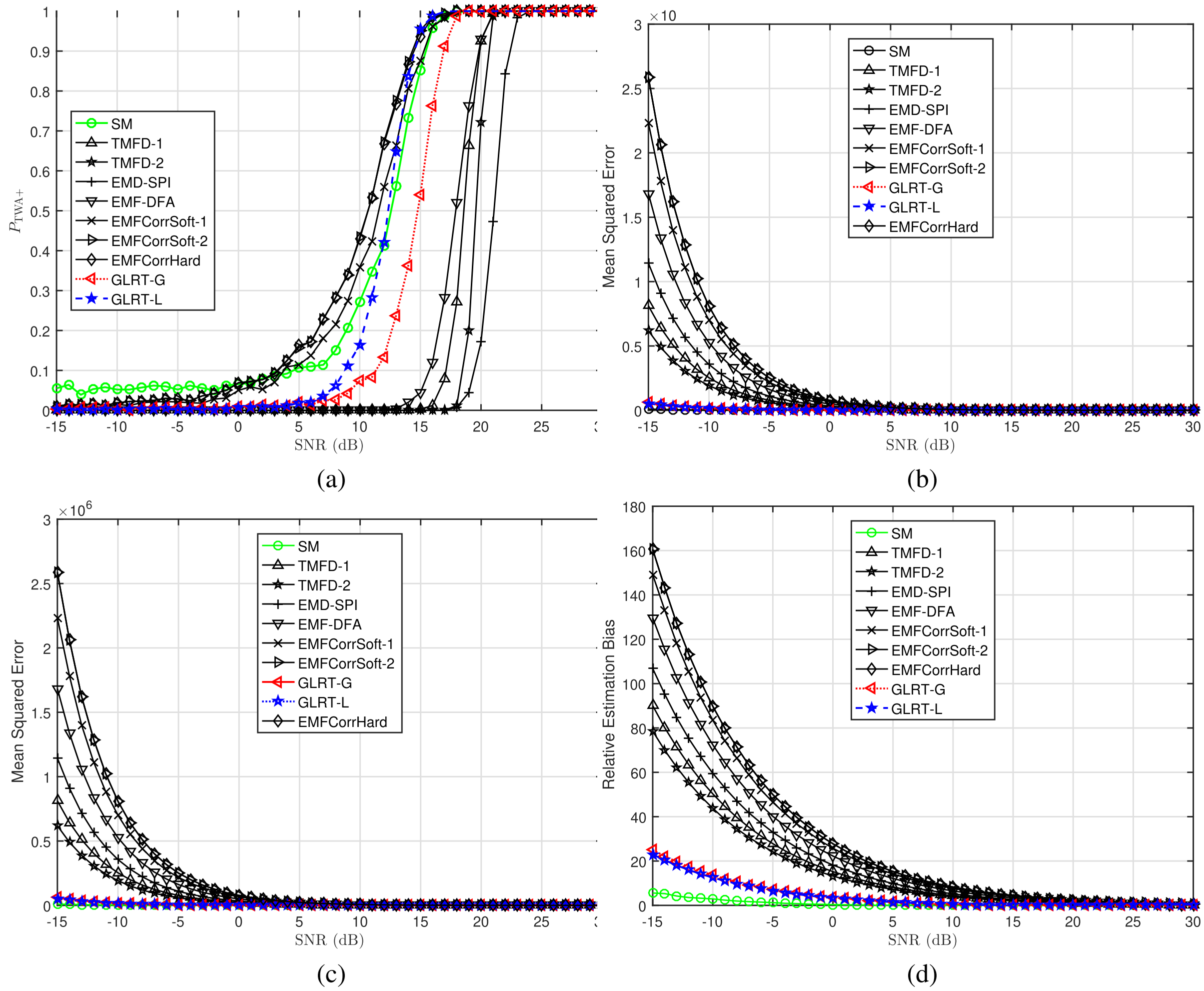

FIGURE 7. GLRT detectors performance for 10 μV TWA under Laplacian noise, (a) Detection (b) Estimation (c) Mean square error (d) Relative estimation bias.

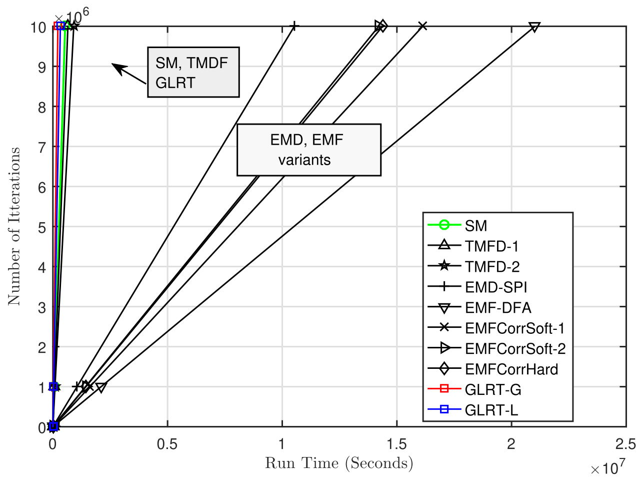

FIGURE 8. Computational analysis Monte Carlo simulations of DTF algorithms.

computationally efficient and lie in the same region as SM and TMF based on mean and median. The run-time analysis of ten detectors and estimators of TWA for Monte Carlo simulations of 10^6 and higher-order is shown in Fig. 8. Time calculations were based on Matlab 2016a on Intel (R) Core (TM) i-7 3740 QM-CPU @ 2.70 GHz, 4GB RAM, and operating on a 64-bit operating system. Although TMF based on mean and median approaches are computationally simpler and resides with GLRT and SM in run time analysis. However, their detection and estimation performance is lower than match filtered based correlation. EMD based match filtering involves decomposition of TWA into IMFs and computations of correlation factors for each gives a good result at very high computation and run time cost. GLRT approaches provide robust estimation under the complete noise spectrum (-30 dB to 15 dB) under DTF with simpler and efficient computation. Estimation of TWA with GLRT detectors can be simulated conveniently, whereas EMD and EMF-based algorithms take much higher time for simulations.

V. CONCLUSION

A generalized detection theoretic framework is proposed for the consolidation of exiting TWA detection and estimation strategies based on signal under noise scenarios. Analytical foundations and comprehensive detection and estimation analysis under a broad spectrum of the noise having Gaussian and Laplacian probability distribution validate GDTF. The study exhibits strengths and limitations of strategies based on statistics, signal decomposition and reconstruction, and likelihood estimation for TWA under process noise artifacts. The research guides in choice of a detector under a noisy environment with computational cost vs TWA analysis strategies with information available about signal and noise. GLRT detectors outperform median and mean templates and correlation-based detection strategies significantly whereas also proves to be computational efficient among all. Template-based strategies are computational intense however gather noise information from signal under observation. GLRT schemes require information regarding TWA acquisition process artifacts i.e., pdf for implementations. The proposed GDTF provides a common platform for further research and exploration of similar work based on TWA process noise statistics in the future.

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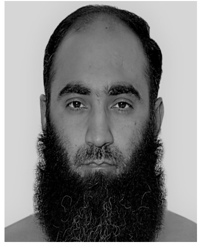

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